CHAPTER 25

Soft-tissue sarcomas

Peter W.T. Pisters, MD, Ephraim S. Casper, MD, Gary N. Mann, MD, Mitchell Weiss, MD, and Brian O'Sullivan, MD

The soft-tissue sarcomas are a group of rare but anatomically and histologically diverse neoplasms. This is due to the ubiquitous location of the soft tissues and the nearly three dozen recognized histologic subtypes of soft-tissue sarcomas. In the United States, approximately 9,400 new cases of soft-tissue sarcoma are identified annually, and about 3,490 patients die of the disease each year. The age-adjusted incidence is 2 cases per 100,000 persons.

Epidemiology

Unlike the more common malignancies, such as colon cancer, little is known about the epidemiology of soft-tissue sarcomas. This, again, reflects the uncommon nature of these lesions.

Gender There is a slight male predominance, with a male-to-female ratio of 1.1:1.0.

Age The age distribution in adult soft-tissue sarcoma studies is < 40 years, 20.7% of patients; 40-60 years, 27.6% of patients; and > 60 years, 51.7% of patients.

Race Studies in large cohorts of patients demonstrate that the race distribution of soft-tissue sarcomas mirrors that of the American population (86% Caucasian, 10% African-American, 1% Asian-American, and 3% other).

Geography Studies have suggested that the incidence and mortality of soft-tissue sarcomas may be increasing in New Zealand. There are no currently available data addressing this possibility in the United States.

Etiology and risk factors

In the majority of cases of patients with soft-tissue sarcoma, no specific etiologic agent is identifiable. However, a number of predisposing factors have been recognized.

Radiation therapy Soft-tissue sarcomas have been reported to originate in radiation fields following therapeutic irradiation for a variety of solid tumors. Frequently, they are seen in the lower-dose regions at the edge of the radiation target volume. By definition, radiation-induced sarcomas arise no sooner than 3 years after radiation therapy and often develop decades later. The majority of these sarcomas are high-grade lesions (90%), and osteosarcoma is a predomi-

nant histology. Malignant fibrous histiocytoma (MFH), angiosarcoma, and other histologic subtypes have also been reported.

Chemical exposure Exposure to various chemicals in specific occupations or situations has been linked with the development of soft-tissue sarcoma. These chemicals include the phenoxy acetic acids (forestry and agriculture workers), chlorophenols (sawmill workers), Thorotrast (diagnostic x-ray technicians), vinyl chloride (individuals working with this gas, used in making plastics and as a refrigerant), and arsenic (vineyard workers).

Chemotherapy Soft-tissue sarcomas have been reported after previous exposure to alkylating chemotherapeutic agents, most commonly after treatment of pediatric acute lymphocytic leukemia. The drugs implicated include cyclophosphamide (Cytoxan, Neosar), melphalan (Alkeran), procarbazine (Matulane), nitrosoureas, and chlorambucil (Leukeran). The relative risk of sarcoma appears to increase with cumulative drug exposure.

Chronic lymphedema Soft-tissue sarcomas have been noted to arise in the chronically lymphedematous arms of women treated with radical mastectomy for breast cancer (Stewart-Treves syndrome). Lower-extremity lymphangiosarcomas have also been observed in patients with congenital lymphedema or filariasis complicated by chronic lymphedema.

Trauma and foreign bodies Although a recent history of trauma is often elicited from patients presenting with soft-tissue sarcoma, the interval between the traumatic event and diagnosis is often short; thus, a causal relationship is unlikely. Chronic inflammatory processes, however, may be a risk factor for sarcoma. Foreign bodies, such as shrapnel, bullets, and implants, have also been implicated.

Signs and symptoms

Signs and symptoms of soft-tissue sarcoma depend, in large part, on the anatomic site of origin. Due to the ubiquitous location of the soft tissues, these malignancies may arise at any site in the body where soft tissues are located. Since 50% of soft-tissue sarcomas arise in an extremity, the majority of patients present with a palpable soft-tissue mass. Pain at presentation is noted in only one-third of cases.

Extremity and superficial trunk Extremity and superficial trunk sarcomas account for 60% of all soft-tissue sarcomas. The majority of patients present with a painless primary soft-tissue mass.

Retroperitoneum Retroperitoneal sarcomas account for 15% of all soft-tissue sarcomas. Most patients (80%) present with an abdominal mass, with 50% of patients reporting pain at presentation. Due to the considerable size of the retroperitoneum and the relative mobility of the anterior intra-abdominal organs, these tumors often grow to substantial size before the patient's nonspecific complaints are evaluated or even before an abdominal mass is noted on physical examination.

Viscera Visceral soft-tissue sarcomas, which comprise 15% of all soft-tissue sarcomas, present with signs and symptoms unique to their viscus of origin. For example, GI leiomyosarcomas or gastrointestinal stromal tumors (GISTs) present with GI symptoms that are usually indistinguishable from those of the more common adenocarcinomas. Similarly, uterine leiomyosarcomas frequently present with painless vaginal bleeding, such as that often noted in patients with more common uterine malignancies.

Head and neck Head and neck sarcomas comprise 10% of all soft-tissue sarcomas. Although generally smaller than sarcomas in other sites, they may present with important mechanical problems related to compression or invasion of adjacent anatomy (eg, orbital contents, airway, or pharynx). In addition, their proximity to critical anatomy can pose management difficulties due to compromise in the delivery of both surgery and radiotherapy.

Pathology

Histopathologic classification As a consequence of the wide spectrum of soft tissues, a variety of histologically distinct neoplasms have been characterized. The current histopathologic classification is based on the putative cell of origin of each lesion. Such classification based on histogenesis is reproducible for the more differentiated tumors. However, as the degree of histologic differentiation declines, it becomes increasingly difficult to determine cellular origin.

In addition, many of these tumors dedifferentiate. This process results in a variety of overlapping patterns, making uniform classification difficult. Experienced soft-tissue pathologists frequently disagree as to the cell of origin of an individual tumor. Comparative studies have demonstrated concordance in histopathologic diagnosis in only two-thirds of cases. MFH used to be the most common histologic subtype of soft-tissue sarcoma. However, in one study, reanalysis histologically, immunohistochemically, and ultrastructurally allowed reclassification in 84% of tumors to a specific line of differentiation.

Assignment of a specific histologic subtype is of secondary importance. This is because, with the possible exceptions of certain small-cell sarcomas, rhabdomyosarcoma, fibrosarcoma, and some forms of angiosarcoma, histogenesis is not directly related to biologic behavior. The propensity for distant metastases and disease-related mortality are best predicted on the basis of histologic grade and tumor size.

Staging and prognosis

AJCC/UICC staging system

The relative rarity of soft-tissue sarcomas, the anatomic heterogeneity of these lesions, and the presence of more than 30 recognized histologic subtypes of variable grade have made it difficult to establish a functional system that can accurately stage all forms of this disease. The revised staging system (6th edition) of the American Joint Committee on Cancer (AJCC) and the Interna-

TABLE 1: AJCC/UICC staging system for soft-tissue sarcomas

Primary tumor (T)		
Tx		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1		Tumor ≤ 5 cm in greatest dimension
	T1a	Superficial tumor[a]
	T1b	Deep tumor[a]
T2		Tumor > 5 cm in greatest dimension
	T2a	Superficial tumor[a]
	T2b	Deep tumor[a]
Regional lymph nodes (N)		
Nx		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Regional lymph node metastasis
Grade (G)		
Gx		Grade cannot be assessed
G1		Well differentiated
G2		Moderately differentiated
G3		Poorly differentiated
G4		Poorly differentiated or undifferentiated (four-tiered systems only)

Stage grouping						
Stage I	T1a-T2b	N0	M0	G1,2	G1	Low
Stage II	T1a-T2a	N0	M0	G3,4	G2,3	High
Stage III	T2b	N0	M0	G3,4	G2,3	High
Stage IV	Any T	N1	M0	Any G	Any G	High or low
	Any T	N0	M1	Any G	Any G	High or low

[a] Superficial tumor is located exclusively above the superficial fascia without invasion of the fascia; deep tumor is located either exclusively beneath the superficial fascia or superficial to the fascia with invasion of or through the fascia. Retroperitoneal, mediastinal, and pelvic sarcomas are classified as deep tumors.

AJCC = American Joint Committee on Cancer; UICC = International Union Against Cancer

From Greene FL, Page DL, Fleming ID, et al (eds): AJCC Cancer Staging Manual, 6th ed. New York, Springer-Verlag, 2002.

tional Union Against Cancer (UICC) is the most widely employed staging classification for soft-tissue sarcomas (Table 1). All soft-tissue sarcoma subtypes are included, except dermatofibrosarcoma protuberans. Four distinct histologic grades are recognized, ranging from well differentiated to undifferentiated.

Histologic grade and tumor size are the primary determinants of clinical stage. Tumor size is further substaged as "a" (a superficial tumor that arises outside the investing fascia) or "b" (a deep tumor that arises beneath the fascia or invades the fascia).

The AJCC/UICC system is designed to optimally stage extremity tumors but is also applicable to torso, head and neck, and retroperitoneal lesions. It should not be used for sarcomas of the GI tract.

A major limitation of the current staging system is that it does not take into account the anatomic site of soft-tissue sarcomas. Anatomic site, however, is an important determinant of outcome. Patients with retroperitoneal, head and neck, and visceral sarcomas have a worse overall prognosis than do patients with extremity tumors. Although the anatomic site is not incorporated as a specific component of any current staging system, outcome data should be reported on a site-specific basis.

Prognostic factors

Understanding relevant clinicopathologic prognostic factors is important in treatment planning for patients with soft-tissue sarcoma. Several reports document the adverse prognostic significance of tumor grade, anatomic site, tumor size, and depth relative to the investing fascia (for extremity and body wall tumors). Patients with high-grade lesions, large (T2) sarcomas, nonextremity subsite, or deep tumor location are at increased risk for disease relapse and sarcoma-specific death.

Sarcoma-specific nomogram Kattan and colleagues from Memorial Sloan-Kettering Cancer Center have developed a sarcoma-specific nomogram for estimation of sarcoma-specific 12-year survival. The nomogram takes into account pretreatment clinicopathologic factors, including anatomic site, histologic subtype, tumor size, histologic grade, tumor depth, and patient age. The nomogram is based on prospectively collected data and has been validated in a population of 2,136 patients with sarcoma. The nomogram can be found on www.nomograms.org and is available in a handheld personal digital assistant version. The sarcoma nomogram may be useful for patient stratification for clinical trials and for risk assessment and treatment planning for individual patients.

Prognostic factors for local vs distant recurrence Unlike other solid tumors, the adverse prognostic factors for local recurrence of a soft-tissue sarcoma differ from those that predict distant metastasis and tumor-related mortality. In other words, patients with a constellation of adverse prognostic factors for local recurrence are not necessarily at increased risk for distant metastasis or tumor-related death. This concept has been recently validated by an analysis of the Scandinavian Sarcoma Group prospective database. In 559 patients with soft-tissue sarcomas of the extremities and trunk treated with surgery alone, inadequate surgical margin was found to be a risk factor for local recurrence but not for distant metastasis. Therefore, staging systems that are designed to stratify patients for risk of distant metastasis and tumor-related mortality using these prognostic factors (such as the AJCC/UICC system) do not stratify patients for risk of local recurrence.

Screening and diagnosis

Currently, there are no screening tests for soft-tissue sarcomas. Since the majority of patients with soft-tissue sarcoma have lesions arising in the extremities or superficial trunk, most of the comments here apply to soft-tissue lesions in

those sites. A separate algorithm is usually employed for the evaluation of a primary retroperitoneal mass or visceral sarcoma.

Physical examination should include an assessment of the size of the mass and its mobility relative to the underlying soft tissues. The relationship of the mass to the investing fascia of the extremity (superficial vs deep) and nearby neurovascular and bony structures should be noted. Site-specific neurovascular examination and assessment of regional lymph nodes should also be performed.

Biopsy Any soft-tissue mass in an adult extremity should be biopsied if it is symptomatic or enlarging, is > 5 cm, or has persisted beyond 4-6 weeks.

Percutaneous approaches Percutaneous tissue diagnosis can usually be obtained with fine-needle aspiration (FNA) for cytology or by percutaneous core biopsy for histology. The needle track should be placed in an area to be excised or that can be encompassed in adjuvant radiotherapy fields if they are to be used. In most instances, when an experienced cytopathologist and/or histopathologist examines the specimen, a diagnosis of malignant soft-tissue sarcoma can be made. FNA is often viewed as a suboptimal method of establishing an initial diagnosis of soft-tissue sarcoma. Histology is usually preferred to cytology because more tissue is obtained, which allows for a more accurate delineation of tumor type and grade. Percutaneous tissue diagnosis is preferred to facilitate subsequent treatment planning and to permit surgical resection to be performed as a one-stage procedure.

Open biopsy In some cases, an adequate histologic diagnosis cannot be secured by percutaneous means. Open biopsy is indicated in these instances, with the exception of relatively small superficial masses, which can be easily removed by excisional biopsy with clear margins.

Biopsies should be incisional and performed with a longitudinal incision parallel to the long axis of the extremity. This approach facilitates subsequent wide local excision of the tumor and the incisional scar and results in minimal difficulties in wound closure. It also facilitates inclusion of any scars within the area of the tumor in adjuvant radiation fields without the excessive morbidity of large-field radiotherapy planning. The incision should be centered over the mass at its most superficial location. It is important to note that care should be taken not to raise tissue flaps. Meticulous hemostasis should be ensured after the biopsy to prevent dissemination of tumor cells into adjacent tissue planes by hematoma.

Retroperitoneal or intra-abdominal mass Biopsy of primary retroperitoneal soft-tissue masses is generally not required for radiographically resectable masses, nor is biopsy recommended for suspected GISTs. The circumstances under which percutaneous or preoperative biopsy of retroperitoneal masses should be strongly considered include:

- tissue diagnosis for radiographically unresectable disease
- clinical suspicion of lymphoma or germ-cell tumor
- tissue diagnosis for neoadjuvant treatment, including radiotherapy and/or chemotherapy
- suspected metastases from another primary tumor.

Primary tumor imaging Optimal imaging of the primary tumor depends on the anatomic site. For soft-tissue masses of the extremities, MRI has been regarded as the imaging modality of choice because it enhances the contrast between tumor and muscle and between tumor and adjacent blood vessels and also provides multiplanar definition of the lesion. However, a recent study by the Radiation Diagnostic Oncology Group that compared MRI and CT in 183 patients with malignant bone and 133 patients with soft-tissue tumors showed no specific advantage of MRI over CT from a diagnostic standpoint.

For pelvic lesions, the multiplanar capability of MRI may provide superior single-modality imaging. In the retroperitoneum and abdomen, CT usually provides satisfactory anatomic definition of the lesion. Occasionally, MRI with gradient sequence imaging can better delineate the relationship of the tumor to midline vascular structures, particularly the inferior vena cava and aorta. In the future, MRI-CT fusion techniques may facilitate treatment planning using conformal radiotherapy techniques.

More invasive studies, such as angiography and cavography, are almost never required for the evaluation of soft-tissue sarcomas.

Imaging for metastatic disease Cost-effective imaging to exclude the possibility of distant metastatic disease depends on the size, grade, and anatomic location of the primary tumor. In general, patients with low-grade or intermediate-/high-grade tumors < 5 cm in diameter require only a chest x-ray for satisfactory staging of the chest. This reflects the fact that these patients are at comparatively low risk of presenting with pulmonary metastases. In contrast, patients with high-grade tumors ≥ 5 cm should undergo more thorough staging of the chest by CT.

Patients with retroperitoneal and intra-abdominal visceral sarcomas should undergo single-modality imaging of the liver to exclude the possibility of synchronous hepatic metastases. The liver is a common site for a first metastasis from these lesions.

Treatment

TREATMENT OF LOCALIZED DISEASE

Surgical resection is the cornerstone of therapy for patients with localized disease. Over the past 20 years, there has been a gradual shift in the surgical management of soft-tissue sarcoma of the extremities away from radical ablative surgery, such as amputation or compartment resection, and toward limb-sparing approaches combining wide local resection with preoperative or postoperative radiotherapy. The development of advanced surgical techniques (eg, microvascular tissue transfer, bone and joint replacement, and vascular reconstruction) and the application of multimodality approaches have allowed most patients to retain a functional extremity without any compromise in survival.

Surgery

The surgical approach to soft-tissue sarcomas depends on careful preoperative staging with MRI or CT for lesions of the extremities and a percutaneous histologic diagnosis and assessment of grade. In most instances, preoperative imaging studies allow for accurate prediction of resectability.

The surgical approach to soft-tissue sarcomas is based on an awareness that these lesions tend to expand and compress tissue planes, producing a pseudocapsule comprising normal host tissue interlaced with tumor fimbriae. Conservative surgical approaches in which the plane of dissection is immediately adjacent to this pseudocapsule, such as intracapsular or marginal excision, are associated with prohibitive local recurrence rates of 33%-63%.

Wide local resection encompassing a rim of normal tissue around the lesion has led to improvements in local control, with local recurrence rates of approximately 30% in the absence of adjuvant therapies. However, studies indicate that carefully selected patients with localized, small (T1), low-grade soft-tissue sarcomas of the extremity can be treated by wide resection alone, with local recurrence rates of < 10%. For example, in a cohort of 56 patients with primarily subcutaneous or intramuscular lesions treated with wide local excision without adjuvant irradiation, 4 local recurrences were noted.

The need for adjuvant irradiation in small (< 5 cm), high-grade lesions has been studied. A retrospective review of 204 patients with stage IIB soft-tissue sarcoma of the extremity treated at Memorial Sloan-Kettering Cancer Center has been completed. A total of 57% of patients did not receive adjuvant radiation therapy, whereas 43% received either brachytherapy or external-beam radiation therapy. With a median follow-up of 67 months, there was no significant difference in 5-year local control, distant replase-free survival, or disease-specific survival when adjuvant irradiation was delivered.

Further studies will be required to define which subsets of patients with primary extremity sarcoma can be treated by wide excision surgery alone. Preoperative or postoperative radiotherapy should be employed for patients with primary T1 sarcomas in whom a satisfactory gross surgical margin cannot be attained without compromise of functionally important neurovascular structures.

Limb-sparing surgery plus irradiation Limb-sparing surgery employing adjuvant irradiation to facilitate maximal local control has become the standard approach for large (T2) soft-tissue sarcomas of the extremities. In most centers, upward of 90% of patients are treated with limb-sparing approaches. Amputation is reserved as a last-resort option for local control and is used with the knowledge that it does not affect survival. This approach was validated in a prospective National Cancer Institute (NCI) study, in which patients with a limb-sparing surgical option were randomized to receive limb-sparing surgery with postoperative radiation therapy or amputation. Both arms of the study included postoperative therapy with doxorubicin, cyclophosphamide, and methotrexate.

Surgical procedure The planned resection should encompass the skin, subcutaneous tissues, and soft tissues adjacent to the tumor, including the previous

biopsy site and any associated drain sites. The tumor should be excised with a 2- to 3-cm margin of normal surrounding tissue whenever possible. Since good adjuvant approaches are available to facilitate local control, this ideal margin is sometimes compromised rather than attempting resection of adjacent, possibly involved bone or neurovascular structures that would result in significant functional loss. In the rare circumstance of gross involvement of neurovascular structures or bone, they can be resected en bloc and reconstructed.

Metal clips should be placed at the margins of resection to facilitate radiation field planning, when and if external irradiation is indicated. Drain sites should be positioned close to the wound to allow inclusion in radiation therapy fields. As noted earlier, avoidance of transverse incisions greatly facilitates the ability to include the tissues at risk in radiation target volume without unduly large fields.

The Netherlands Cancer Institute published its results in patients with unresectable soft-tissue sarcoma of the extremities who were perfused with melphalan and TNF-alpha. A total of 49 patients were treated and followed for a median of 26 months. One patient died shortly after perfusion, but 31 patients (63%) were able to undergo resection of the tumor. Based on clinical and pathologic grounds, an overall response was seen in 31 patients (63%), and a complete response was seen in 4 patients (8%). A total of 28 patients (57%) had local control with limb preservation. Toxicity was frequent but usually mild (*Noorda EM, Vrouenraets BC, Nieweg OE, et al: Cancer 98:1483-1490, 2003*).

Regional lymphadenectomy Given the low, 2%-3%, prevalence of lymph node metastasis in adult sarcomas, there is no role for routine regional lymphadenectomy. Patients with angiosarcoma, embryonal rhabdomyosarcoma, synovial sarcoma, and epithelioid histologies have an increased incidence of lymph node metastasis and should be carefully examined and radiographically imaged for lymphadenopathy. Clinically apparent lymphadenopathy should be treated with therapeutic lymphadenectomy. A recent analysis suggested that select patients undergoing lymphadenectomy, particularly in the absence of systemic metastases, may have a 5-year survival rate of 57%.

Radiotherapy

Scheduling Radiation therapy is usually combined with surgical resection in the management of patients with soft-tissue sarcomas of the extremities. The decision of whether to use preoperative (neoadjuvant) or postoperative (adjuvant) irradiation remains controversial and has been addressed in a phase III randomized trial.

Preoperative irradiation has a number of theoretic and practical advantages: (1) Smaller radiation portals can be utilized, as the scar, hematomas, and ecchymoses do not need to be covered. (2) Preoperative irradiation may produce tumor encapsulation, facilitating surgical resection from vital structures. (3) It is easier to spare a strip of skin and thereby reduce the risk of lymphedema. (4) The size of the tumor may be reduced, thus decreasing the extent of surgical resection. (5) Lower radiation doses can be utilized, as there are fewer relatively radioresistant hypoxic cells.

Preoperative irradiation also has several drawbacks, however. They include (1) the inability to precisely stage patients based on pathology due to downstaging and (2) increased problems with wound healing.

Studies of preoperative irradiation from the University of Florida, M. D. Anderson Cancer Center, and Massachusetts General Hospital demonstrated local control rates of 90% using doses of approximately 50 Gy. Survival depended on the size and grade of the primary tumor. Distant metastases were the primary pattern of failure.

Postoperative irradiation A number of retrospective reports, as well as a randomized trial from the NCI, have demonstrated that limb-sparing surgery plus postoperative irradiation produces local control rates comparable to those achieved with amputation. Five-year local control rates of 70%-90%, survival rates of 70%, and limb-preservation rates of 85% can be expected.

Equivocal or positive histologic margins are associated with higher local recurrence rates, and, therefore, adjuvant external-beam irradiation should be considered in all patients with sarcoma of the extremities with positive or close microscopic margins in whom reexcision is impractical. Postoperative doses of 60-65 Gy should be used.

Interstitial therapy with iridium-192 is used at some institutions as a radiation boost to the tumor bed following adjuvant external-beam irradiation. At Memorial Sloan-Kettering Cancer Center, adjuvant brachytherapy is often used in place of external irradiation. In a randomized trial, the 5-year local control rate was 82% in patients who received adjuvant brachytherapy, vs 69% in those treated with surgery alone. On subset analysis, the local control rate was found to be 89%, vs 66% in those patients with high-grade lesions. This study and further studies have indicated that brachytherapy has no impact on local control for low-grade lesions.

If an implant alone is used, the dose is 40-45 Gy to a volume that includes all margins; when a boost is combined with additional external-beam irradiation, a dose of 20-25 Gy is utilized. Some data suggest a higher rate of wound complications and a delay in healing when implants are afterloaded prior to the third postoperative day. Although some centers load implants sooner, this step must be performed with caution and strict attention to the incision site.

Over a 15-year period, 202 patients with high-grade sarcoma of the extremities underwent complete gross resection and adjuvant brachytherapy to a median dose of 45 Gy, delivered over 5 days. With a median follow-up of 61 months, the 5-year local control, distant relapse-free survival, and overall survival rates were 84%, 63%, and 70%, respectively. These rates compared favorably with data on external-beam irradiation. Morbidity of brachytherapy was considered acceptable, with reoperation rates of 12%, bone fractures in 3%, and nerve damage in 5%.

Comparison of irradiation techniques Comparable local control results (90%) are obtained with preoperative, postoperative, and interstitial techniques, although rates of wound complications are higher with preoperative techniques.

Brachytherapy can offer a number of advantages. When brachytherapy is employed as the sole adjuvant, the entire treatment (surgery and irradiation) is completed in a 10- to 12-day period, compared with the 10-12 weeks required for typical external-beam irradiation (6-7 weeks) and surgery (4- to 6-week break before or after irradiation). Generally, smaller volumes can be irradiated with brachytherapy, which could improve functional results. However, smaller volumes may not be appropriate, depending on the tumor size, grade, and margin status.

The 5-year results of the NCI of Canada Clinical Trials Group phase III randomized trial of preoperative vs postoperative radiotherapy in extremity soft-tissue sarcomas were reported at the ASCO 2004 meeting. A total of 190 patients were randomized to receive treatment (94 preoperative and 96 postoperative irradiation). The updated results continue to show no difference in local control, metastatic relapse-free survival, and recurrence-free survival. The previously reported difference in overall survival has not been seen with longer follow-up. The 5-year overall survival rate was 73% vs 67% (P = .48). Tumor size and grade were the only significant predictors for metastatic relapse, overall survival, and cause-specific survival (*O'Sulllivan B, Davis A, Turcotte R, et al: J Clin Oncol [abstract] 22:14S, 2004*).

The National Cancer Institute of Canada Clinical Trials Group published 3-year median follow-up results of a randomized phase III trial comparing preoperative with postoperative radiotherapy for limb soft-tissue sarcoma (Figures 1A-1D). Wound complications were observed in 31 of 88 patients (35%) in the preoperative group and 16 of 94 patients (17%) in the postoperative group (difference, 18% [95% CI: 5-30]; $P = .01$). Tumor size and anatomical site were also significant risk factors in multivariate analysis. Local control was identical in both arms of the trial. Five-year outcomes have recently been reported, and no difference in metastases, cause-specific survival, or overall survival was noted. Because preoperative radiotherapy is associated with a greater risk of wound complications than postoperative radiotherapy, but less late fibrosis and edema, the choice of regimen for patients with soft-tissue sarcoma should take into account the timing of surgery and radiotherapy and the size and anatomic site of the tumor.

Regardless of the technique employed, local control is a highly achievable and worthwhile end point, as demonstrated in a study of 911 patients treated by various techniques at Memorial Sloan-Kettering Cancer Center. Of the 116 patients who developed a local recurrence, 38 patients subsequently developed metastases and 34 patients died. Metastases after local recurrence were predicted in patients with high-grade or large (> 5 cm) tumors.

Treatment recommendations Adjuvant radiotherapy should be employed for virtually all high-grade sarcomas of the extremities and larger (≥ 5 cm) low-grade lesions. If small (T1) lesions can be resected with clear margins, radiotherapy can be omitted. Postoperative therapy with either external-beam irradiation (with or without an interstitial implant boost) or an implant alone will achieve a high likelihood of local control and, therefore, limb preservation. Preoperative irradiation, although equally efficacious, does carry a higher wound complication rate than the postoperative approach.

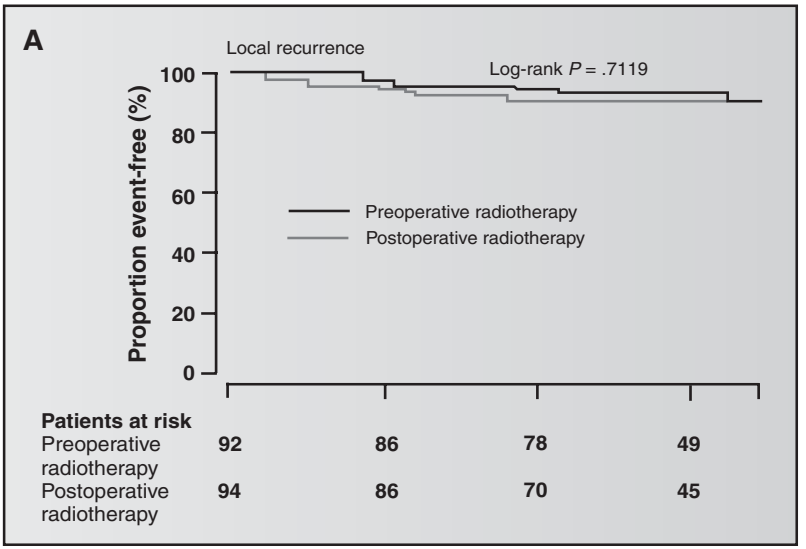

FIGURE 1A: Kaplan-Meier plots for probability of local recurrence in the National Cancer Institute of Canada Clinical Trials Group phase III trial.

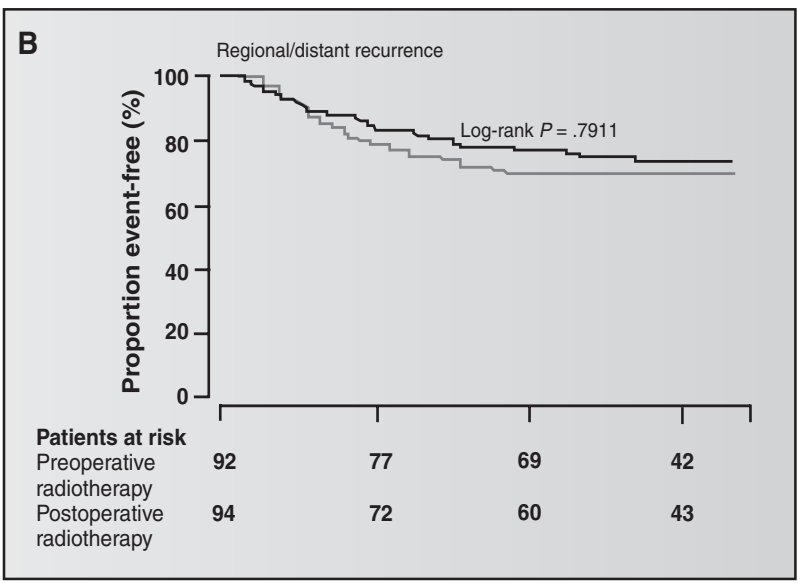

FIGURE 1B: Kaplan-Meier plots for probability of metastatic (regional and distant) recurrence in the National Cancer Institute of Canada Clinical Trials Group phase III trial.

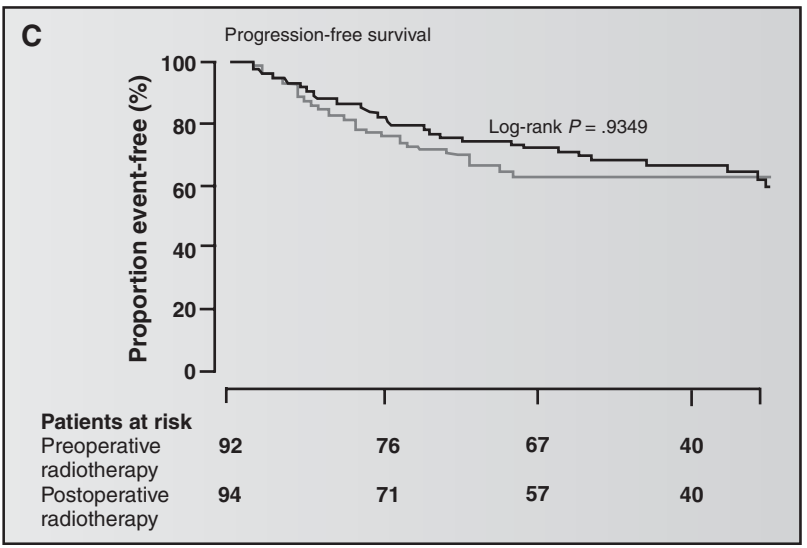

FIGURE 1C: Kaplan-Meier plots for probability of progression-free survival in the National Cancer Institute of Canada Clinical Trials Group phase III trial.

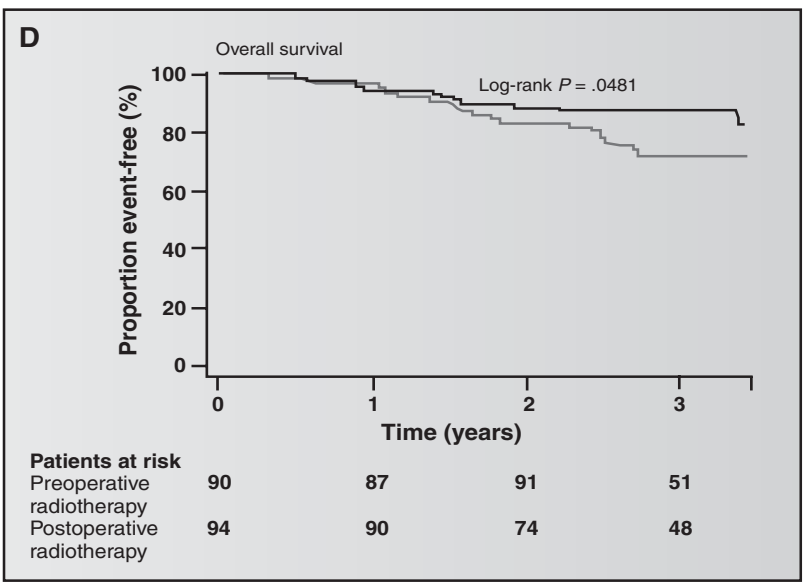

FIGURE 1D: Kaplan-Meier plots for probability of overall survival in the National Cancer Institute of Canada Clinical Trials Group phase III trial.

From O'Sullivan R, Davis AM, Turcotte R, et al: Lancet 359:2235–2241, 2002.

Primary radiation therapy

Several studies on radiation therapy alone in the treatment of unresectable or medically inoperable soft-tissue sarcomas have reported 5-year survival rates of 25%-40% and local control rates of 30%. Local control depends largely on the size of the primary tumor. Radiation doses should be at least 65-70 Gy, if delivery of such doses is feasible. The tumor's location may be particularly important in determining this dose because of the potential for damage to critical structures (eg, the spinal cord) by the higher doses normally used.

Radiation therapy in retroperitoneal sarcomas

Only 50% of patients with retroperitoneal sarcomas are able to undergo complete surgical resection. Of patients undergoing complete resection, one-half develop local recurrence. This significant local failure rate suggests a potentially important role for adjuvant treatment in all patients with retroperitoneal sarcomas. However, the role of radiation therapy in the treatment of retroperitoneal sarcomas remains controversial due to the rarity of the tumor, the paucity of data, the retrospective nature of available studies, the low doses of radiation used in many studies, and the lack of consistent policies in determining the indications for radiation therapy.

Postoperative irradiation Two-year local control rates of 70% have been reported with the addition of postoperative irradiation. However, irradiation of the retroperitoneum/abdomen in doses that have effected local control in soft-tissue sarcoma of the extremities (50-65 Gy) is usually associated with significant GI toxicity. Obviously, the incidence of GI toxicity depends on the exact fields and technique used. However, as most retroperitoneal sarcomas are $>$ 10-15 cm, the radiation fields employed are generally also quite large, and bowel is often located and/or tethered in the high-risk area. Three-dimensional treatment planning and conformal techniques can now be utilized to maximize the radiation dose to the tumor bed while minimizing the dose to the surrounding normal tissues.

Preoperative irradiation The advantages of preoperative radiotherapy have already been discussed for soft-tissue sarcomas of the extremities. In the retroperitoneum, an additional advantage is that bowel is frequently displaced significantly by the tumor. In contrast to the postoperative setting, the bowel being treated is also unlikely to be tethered by adhesions from prior surgery. These features significantly offset acute toxicity of large-field intra-abdominal radiotherapy (eg, nausea, vomiting, and diarrhea) as well as the potential for late-onset bowel toxicity. Conformal techniques capable of sparing normal tissues are also more easily applied in the preoperative setting, when the tumor can be visualized and the target area more readily defined. The American College of Surgeons Oncology group (ACSOG) has recently opened a prospective, randomized trial (ACSOG 2 9031) investigating this very issue. In this phase III study, patients will be randomized to undergo surgical resection of the retroperitoneal tumor alone vs preoperative irradiation followed by surgical resection.

Intraoperative irradiation In a prospective trial from the NCI, 35 patients with completely resected retroperitoneal sarcomas were randomized to receive either intraoperative electron-beam irradiation (IORT) followed by low-dose (30-40 Gy) postoperative external-beam irradiation or high-dose postoperative external-beam irradiation (35-40 Gy plus a 20-Gy boost). Absolute local recurrence rates were significantly lower in the IORT group ($P < .05$), but disease-specific and overall survival rates did not differ between the two groups.

Similarly, a nonrandomized series from the Massachusetts General Hospital has suggested improved local control with IORT for patients with retroperitoneal sarcoma. In 16 patients who underwent irradiation, complete gross resection, and IORT, overall survival and local control rates were 74% and 83%, respectively. These numbers diminished to 30% and 61%, respectively, in the 13 patients treated with irradiation and complete gross resection without IORT. Although these local control results are encouraging, IORT remains investigational and cannot be advocated on a routine basis at this time.

Isolated limb perfusion

Recent studies have evaluated the role of isolated limb perfusion (ILP) in the management of sarcomas of the extremities. These studies have generally been extrapolations from protocols initially designed to treat locally advanced melanoma.

The agents most commonly employed for ILP have been melphalan and tumor necrosis factor-alpha (TNF-α), with or without interferon-gamma (IFN-γ-1b [Actimmune]). The results of the largest series of ILP in patients with locally advanced soft-tissue sarcoma of the extremities were reported by Eggermont and colleagues. TNF has now been approved in Europe for ILP in patients with locally advanced, grade 2/3 soft-tissue sarcomas of the extremities.

ROLE OF ADJUVANT CHEMOTHERAPY

The striking success of combined-modality therapy in children with osteogenic sarcoma, embryonal rhabdomyosarcoma, and the Ewing's sarcoma family of tumors has provided the stimulus for the use of aggressive combined-modality approaches in adults. The literature is replete with reports of the apparent benefit of combined-modality therapy in patients with resectable soft-tissue sarcoma. Yet most series are either retrospective or small nonrandomized trials.

Postoperative chemotherapy

A number of published trials have compared postoperative chemotherapy with observation alone in adults who had undergone resection of a primary or recurrent soft-tissue sarcoma. Most of these trials included fewer than 100 patients, and even the largest trial had inadequate statistical power to detect a 15% difference in survival. Other flaws confound the interpretation of many of the studies. Some trials included low-risk patients with small and/or low-grade sarcomas. In some trials, patient ineligibility rates were as high as 20%, and in none of the trials published before 2000 was ifosfamide (Ifex) part of the combination evaluated.

In five of the six trials in which doxorubicin monotherapy was studied, including one study limited to patients with uterine sarcoma, a significant improvement in survival could not be demonstrated. Among the trials of combination chemotherapy, most used the combination known as CyVADIC (cyclophosphamide, vincristine, Adriamycin [doxorubicin], and dacarbazine [DTIC-Dome]). A significant survival advantage was seen only in one combination chemotherapy trial.

Nonetheless, some of the trials showed a trend or a statistically significant improvement in disease-free survival among patients who were administered adjuvant chemotherapy, especially among those with high-grade sarcomas of the extremities. Analyses of the pooled results of the published literature are consistent with this observation.

SMAC meta-analysis A formal meta-analysis of individual data from 1,568 patients who participated in randomized trials of postoperative adjuvant chemotherapy vs no chemotherapy control patients was performed by the Sarcoma Meta-Analysis Collaboration (SMAC). Although not all data were available for all patients, the analysis demonstrated a significant reduction in the risk of local or distant recurrence in patients who received adjuvant chemotherapy.

The overall hazard ratio for distant relapse-free survival was 0.70; ie, the risk of distant relapse (metastasis) was reduced by 30% in treated patients. The absolute benefit at 10 years was 10%, so the recurrence-free survival rate at 10 years was improved from 60% to 70%. Also, the hazard ratio for local recurrence-free survival was 0.73 (27% reduction in the risk of local recurrence), and the absolute benefit was 6%.

The hazard ratio for overall survival, however, was 0.89, which did not meet the criteria for statistical significance. The observed survival at 10 years was 54% for patients who received chemotherapy and 50% for those who did not. Subset analysis failed to show that the effects of chemotherapy differed by primary site, although the best evidence for an effect of adjuvant chemotherapy was seen in patients with sarcoma of the extremities.

Ifosfamide-containing trials Only one trial included in the meta-analysis used an ifosfamide-containing regimen; that trial involved only 29 patients. An attempt to conduct a large prospective trial of postoperative chemotherapy with the MAID (mesna [Mesnex], Adriamycin [doxorubicin], ifosfamide, and dacarbazine) regimen in the United States failed because of insufficient patient accrual.

An Italian cooperative group conducted a trial in which patients 18-65 years old with high-grade (≥ 5 cm) or any recurrent sarcoma of the extremities were randomized to receive postoperative chemotherapy or observation alone. The treatment consisted of five cycles of epirubicin (Ellence), 60 mg/m^2 on days 1 and 2, plus ifosfamide, 1.8 gm/m^2 on days 1-5. Granulocyte colony-stimulating factor (G-CSF, filgrastim [Neupogen]) was used to support the granulocyte counts during therapy.

The trial had been planned for 200 patients but was interrupted after accrual of 104 patients, when an interim analysis showed a significant survival advantage for the chemotherapy-treated group. At 36 months after the last randomiza-

tion, with a median follow-up of 59 months, median overall survival among the patients who received adjuvant chemotherapy was 75 months, vs 46 months in control patients ($P = .03$).

The updated results of the Italian Cooperative Group trial were recently published. With a median follow-up of 89.6 months, the difference in overall survival in the two groups is no longer statistically significant. However, the 5-year overall survival was 66% in those who received adjuvant chemotherapy (epirubicin [60 mg/m^2] and ifosfamide [1.8 g/m^2]), vs 46% in the control group ($P = .04$; *Frustaci S, De Paoli A, Bidoli E, et al: Oncology 65[suppl 2]:80-84, 2003*).

Preoperative chemotherapy

Preoperative chemotherapy has been adopted at many centers for patients with large high-grade sarcoma. The specific regimens employed have evolved over the years but generally contain both an anthracycline and ifosfamide. Some investigators have added concurrent, sandwiched or sequential preoperative radiation therapy in nonrandomized trials. European investigators have also explored combination chemotherapy with regional hyperthermia.

Aside from theoretic considerations, there are several pragmatic reasons to favor preoperative over postoperative treatment. First, a reduction in the size of a large lesion may permit surgical resection with less morbidity. Second, compliance may be better with preoperative therapy. One observation that supports the neoadjuvant approach is that response to preoperative chemotherapy, whether pathologic or radiographic, predicts improved tumor control and survival.

Neoadjuvant chemotherapy has been explored in a prospective randomized trial initiated by the EORTC (European Organization for Research on the Treatment of Cancer). The trial was open to patients who had a sarcoma measuring at least 8 cm (of any grade), a primary or recurrent intermediate- to high-grade (grade 2/3) sarcoma of any size, or a locally recurrent or inadequately excised grade 2/3 sarcoma. In spite of these broad eligibility criteria, accrual was slow, and the trial was closed after only 150 patients entered.

Patients were randomized to receive either immediate surgery, followed by radiation therapy for close or positive margins, or three cycles of chemotherapy with doxorubicin (50 mg/m^2 by IV bolus) plus ifosfamide (5 g/m^2 by 24-hour continuous infusion) with mesna. Among the 134 eligible patients, over 80% had primaries of the extremities, but only 4% had grade 2/3 lesions > 8 cm. Among 49 patients assessable for response, 29% had major objective responses, including 4 complete responses. Only 18% had progression of disease before surgery. Chemotherapy was generally well tolerated and never prevented surgery. With a median follow-up of 7.3 years, the estimated 5-year survival rate among the 67 surgery-alone patients was 64% and among the neoadjuvant chemotherapy patients was 65% ($P = .22$).

More recently, there have been trials exploring the role of neoadjuvant chemotherapy and radiation therapy to decrease the rate of distant failure and possibly impact survival. A study reported from Massachusetts General Hospital enrolled patients with high-grade soft-tissue sarcomas (8 cm or larger). Patients were treated with three cycles of preoperative chemotherapy consisting of mesna, Adriamycin (doxorubicin), ifosfamide, and dacarbazine (MAID) interdigitated

with 44 Gy of radiation therapy. This reigmen was followed by surgical resection and three cycles of postoperative MAID chemotherapy. In cases with positive surgical margins, an additional 16 Gy of radiation therapy was delivered.

This regimen resulted in a significant improvement in 5-year freedom from distant metastasis (75% vs 44%, $P = .0016$) when compared with historic control patients. Additionally, 5-year disease free and overall survival rates were 70% vs 42% ($P = .0002$) and 87% vs 58% ($P = .0003$) for the MAID and control groups, respectively. There was a 29% rate of wound healing complications in the MAID group.

The M. D. Anderson Cancer Center conducted a phase I trial to define the maximum tolerated dose of continuous infusion doxorubicin administered with preoperative radiation therapy to a dose of 50 Gy. A total of 27 patients with intermediate- or high-grade sarcomas were enrolled in the trial. The maximum tolerated dose of doxorubicin was 17.5 mg/m^2/wk. Twenty-six patients underwent surgery, and all had a macroscopic complete resection (R0 or R1). Two patients had a pathologic complete response. These studies suggest that further investigation of a preoperative approach combining chemotherapy and radiation therapy is warranted.

Treatment recommendations

- Multidisciplinary treatment planning should precede the initiation of any therapy. An experienced multidisciplinary team should evaluate pathologic material and imaging studies and coordinate the integration of surgical resection, irradiation, and systemic therapy.
- Ideally, patients should be offered participation in clinical trials. Unfortunately, there are no active trials in the United States that will definitively answer the most important questions. Thus, a decision to treat must be made on an individual basis.
- Preoperative chemotherapy should be considered for fit, high-risk patients after a discussion of the risks and potential benefits. Older patients, especially those with cardiac or renal disease, are not optimal candidates for such treatment.
- Patients who do not receive preoperative chemotherapy may still be offered postoperative treatment. Adjuvant doxorubicin/ifosfamide combinations may improve relapse-free survival in carefully selected patients and can be considered for the treatment of those with tumor size > 5 cm, deep tumor location, and high histologic grade.
- For patients who opt for preoperative or postoperative chemotherapy, a regimen that includes doxorubicin (60-75 mg/m^2) or epirubicin (120 mg/m^2) plus ifosfamide (9-10 g/m^2) or the MAID regimen (see the section on "Combination chemotherapy"), given for a total of five cycles, would be a reasonable choice.
- Outside the context of a clinical trial, concurrent chemotherapy and irradiation should be avoided.

TREATMENT OF LOCAL RECURRENCE

Despite optimal multimodality therapy, local recurrence develops in 10%-50% of patients, with a median local recurrence-free interval of ~24 months. Local recurrence rates are a function of the primary site and are highest for retroperitoneal and head and neck sarcomas, for which adequate surgical margins are difficult to attain. In addition, high-dose adjuvant irradiation of these sites is often limited by the relative radiosensitivity of surrounding structures. These factors result in local recurrence rates of 40% for retroperitoneal sarcomas and up to 50% for head and neck sarcomas, which are substantially higher than the 10% proximity typically seen for extremity sarcomas.

A recent large retrospective analysis of patients with high-grade sarcoma of the extremities was reported from UCLA. Local recurrence required amputation in 38% of cases and was associated with a threefold decrement in survival. This finding accentuates the necessity for adequate local therapy for sarcomas presenting primarily as well as for multidisciplinary management of local recurrence.

Reoperation Following staging evaluation, patients with isolated local recurrence should undergo reoperation. The results of reoperation in this setting are good, with two-thirds of patients experiencing long-term survival.

Adjuvant radiation therapy If no prior radiation therapy was employed, adjuvant irradiation (50-65 Gy) should be used before or after surgery for locally recurrent disease. Radiation therapy (external-beam irradiation or brachytherapy) should be considered in patients for whom previous radiation doses were subtherapeutic or the previous radiation field design permitted additional treatment.

Reports from Memorial Sloan-Kettering Cancer Center, M. D. Anderson Cancer Center, and Princess Margaret Hospital suggest that patients who develop local recurrence following previous full-dose irradiation represent a difficult local control challenge. A report from Memorial Sloan-Kettering Cancer Center suggests that limb-sparing surgery combined with adjuvant brachytherapy may produce excellent local control and function in this group.

ILP Ongoing clinical investigations are defining the role of ILP in the management of patients with locally recurrent sarcoma.

TREATMENT OF LIMITED PULMONARY METASTASIS

Thoracotomy and metastasectomy The most common site of metastatic disease involvement of soft-tissue sarcoma is the lungs. Rates of 3-year survival following thoracotomy for pulmonary metastasectomy range from 23%-42%. This fact, combined with the limited efficacy of systemic therapy, is the basis for the recommendation that patients with limited pulmonary metastases and no extrapulmonary disease should undergo thoracotomy and metastasectomy.

Appropriate patient selection for this aggressive therapeutic approach to metastatic disease is essential. The following are generally agreed upon criteria: (1) the primary tumor is controlled or controllable; (2) there is no extrathoracic meta-

static disease; (3) the patient is a medical candidate for thoracotomy; and (4) complete resection of all disease appears to be possible.

Preresection chemotherapy Chemotherapy is often recommended before resection of pulmonary metastases. However, there are no convincing data to support this approach.

CHEMOTHERAPY FOR UNRESECTABLE LOCALLY ADVANCED OR METASTATIC DISEASE

Single agents

Doxorubicin Early trials of doxorubicin reported major responses in approximately 30% of patients with advanced soft-tissue sarcoma. In more recent randomized series, however, the rate of response has been closer to 17%.

Subset analysis of patients with soft-tissue sarcoma from a broad phase II trial in which patients were randomized to receive various doses of doxorubicin demonstrated a steep dose-response relationship; patients treated with doses < 60 mg/m^2 rarely responded. Whether dose intensification of doxorubicin is associated with improved survival remains an open question (see section on "Intensifying chemotherapy").

Pegylated liposomal doxorubicin (Doxil in the United States, Caelyx in Europe) has demontrated limited activity in phase II trials, especially in patients whose disease is refractory to standard doxorubicin. In a randomized comparison among 95 previously untreated patients, however, the response rates to pegylated liposomal doxorubicin (50 mg/m^2 every 4 weeks; 10%) and to standard doxorubicin (75 mg/m^2 every 3 weeks; 9%) were similar, with no significant difference in time to disease progression or survival. Response rates improved to 14% and 12%, respectively, when GIST cases were excluded.

Ifosfamide In a randomized phase II trial conducted by the EORTC, 18% of patients treated with ifosfamide (5 g/m^2) experienced major responses, in contrast to 12% of patients treated with cyclophosphamide (1.5 g/m^2), despite the greater myelosuppression with the latter agent. In a large American phase II trial, 17 of 99 patients with soft-tissue sarcoma responded to ifosfamide (8 g/m^2). All of the patients had been treated previously with doxorubicin-based therapy, suggesting a degree of non–cross-resistance.

Increasing ifosfamide dose Responses to ifosfamide (≥ 12 g/m^2) have been observed in patients whose disease progressed while receiving lower doses, supporting the concept of a dose-response relationship.

In a randomized trial, the response to 9 g/m^2 of ifosfamide (17.5%) was superior to the 3% response observed among patients treated with 5 g/m^2. The reason for the low response to the lower dose was unclear. In a subsequent trial by the same investigators, the response to 12 g/m^2 was only 14%, however.

Among 45 "assessable" patients enrolled in a Spanish phase II trial of ifosfamide (14 g/m^2 given by continuous infusion over 6 days), the response rate was 38%, but 47% of patients developed febrile neutropenia and 32%, grade 3 neurotoxicity.

At M. D. Anderson Cancer Center, ifosfamide (14 g/m^2 given by continuous infusion over 3 days) yielded responses in 29% of 37 patients with soft-tissue sarcoma and 40% of patients with bone sarcoma. Also within that report was a small cohort of patients in whom the response to the same total dose of ifosfamide was higher when the drug was given by an intermittent bolus rather than a continuous infusion; this finding led the authors to suggest that bolus therapy is more efficacious than continuous infusion. Pharmacokinetic studies, however, have shown no difference between a 1-hour infusion or bolus injection of ifosfamide with respect to the area under the curve for serum ifosfamide or its metabolites or the levels of ifosfamide metabolites in urine.

In an EORTC phase II trial, ifosfamide (12 g/m^2 given as a 3-day continuous infusion every 4 weeks) yielded a response rate of 17% among 89 chemotherapy-naive patients and 16% among 25 previously treated patients.

Ifosfamide doses as high as 14-20 g/m^2 have been given with hematopoietic growth factor support; reported response rates are high, but neurologic and renal toxicities often are dose-limiting. The available data suggest that synovial sarcoma is particularly sensitive to ifosfamide.

An ongoing randomized phase II study is evaluating the efficacy of trabectedin (Yondelis) in the treatment of patients with soft-tissue sarcoma refratory to conventional chemotherapy. The study has accrued 60 patients with leiomyosarcoma or liposarcoma to date who have been assigned to one of two treatment arms: trabectedin as a 3-h infusion every week for 3 consecutive weeks of a 4-week cycle (arm A) or as a 24-h IV infusion every 3 weeks (arm B). All patients were pretreated with dexamethasone. Of these 60 patients, 29 are evaluable. Activity has been noted in both arms, with three patients in arm B demonstrating a partial response. Tolerability appears to be consistent with prior experience with this agent (*Samuels BL, Rushing D, Chawla SP, et al: Proc Am Soc Clin Oncol [abstract] 23:814, 2004*).

Dacarbazine The activity of dacarbazine in soft-tissue sarcoma has been recognized since the 1970s and was confirmed in a formal phase II trial. This marginally active agent has been used mostly in doxorubicin-based combinations.

Ecteinascidin (ET-743, trabectedin [Yondelis]), a novel compound derived from a marine organism, has demonstrated promising activity as well. In phase I trials, ET-743 demonstrated activity in heavily pretreated patients with advanced sarcoma. Two phase II trials of ET-743 (1,500 mg/m^2 over 24 hours every 3 weeks) in refractory non-GIST soft-tissue sarcoma have been reported. In one trial, 2 partial responses and 4 minor responses were seen among 52 patients; 9 additional patients had stable disease for at least 6 months. Twenty-four percent of patients were disease progression free at 6 months. Median survival was 12.8 months, with 30% of patients alive at 2 years. In the other trial, responses were observed in 3 of 36 patients, with 1 complete response and 2 partial responses, for an overall response rate of 8% (95% CI: 2-23). Responses, however, were durable, lasting up to 20 months. The predominant toxicities were neutropenia and elevation of transaminase levels. Two phase II trials of ET-743 in patients with GIST showed no therapeutic activity.

TABLE 2: Chemotherapy regimens for soft-tissue sarcoma

Drug/combination	Dose and schedule
AD (96-hour infusional)	
Adriamycin (doxorubicin)	15 mg/m^2/d for 4 days (96-hour continuous infusion), total dose of 60 mg IV over 4 days
Dacarbazine	250 mg/m^2/d for 4 days (96-hour continuous infusion), total dose of 1,000 mg/m^2 IV over 4 days
Repeat cycle every 21 days.	
Antman K, Crowley J, Balcerzak SP, et al: J Clin Oncol 11:1276–1285, 1993.	
AD (bolus)	
Adriamycin (doxorubicin)	60 mg/m^2 on day 1 by rapid IV infusion
Dacarbazine	750 mg/m^2 on day 1 by rapid IV infusion
Repeat cycle every 21 days.	
NOTE: Bolus dosage was compared with Adriamycin (doxorubicin) at 60 mg/m^2 and dacarbazine at 750 mg/m^2 delivered by continuous IV infusion for 96 hours on days 1-4. The median survival times between the two treatment arms were equivalent, with the toxic effects being milder in the infusional dosage.	
Zalupski M, Metch B, Balcerzak S, et al: J Natl Cancer Inst 83:926–932, 1991.	
AIM	
Adriamycin (doxorubicin)	30 mg/m^2 IV on days 1 and 2 by rapid IV infusion
Ifosfamide	3,750 mg/m^2 on days 1 and 2 by IV infusion over 4 hours
Mesna	750 mg/m^2 IV infused immediately preceding and 4 and 8 hours after ifosfamide administration on days 1 and 2
Repeat cycle every 21 days.	
NOTE: IV hydration at 300 mL/h beginning 3 hours before each treatment cycle and for 3 days at 100 mL/h after each day-1 ifosfamide infusion. Granulocyte colony-stimulating factor, 5 μg/kg subcutaneously, may be given starting 24-48 hours daily for 10 days or until a granulocyte count of 1,500/μL is reached. Appropriate supportive measures should be given.	
Edmonson JH, Ryan LM, Blum RH, et al: J Clin Oncol 11:1269–1275, 1993.	

Other agents Gemcitabine (Gemzar) has demonstrated modest activity in several phase II trials, although results of a recent Southwest Oncology Group (SWOG) trial were disappointing. Taxanes, vinca alkaloids, and platinum compounds have demonstrated only marginal activity, however. It should be noted that the taxanes, gemcitabine, and vinorelbine have been observed to be active in angiosarcoma, especially angiosarcoma involving the scalp and face.

Combination chemotherapy

Combination chemotherapy regimens have been used widely in the management of patients with soft-tissue sarcoma. High response rates have been reported in a number of single-arm phase II trials. Most combination regimens include an anthracycline (either doxorubicin or epirubicin) plus an

Drug/combination	Dose and schedule
EIM	
Epirubicin	60 mg/m^2 IV infused on days 1 and 2, total dose of 120 mg/m^2 per cycle
Ifosfamide	1.8 g/m^2/d on days 1-5, total dose of 9 g/m^2 per cycle
Mesna	360 mg/m^2 IV infused immediately before and 4 and 8 hours after ifosfamide infusion
Repeat cycle every 3 weeks for a total of 5 cycles.	
Granulocyte colony-stimulating factor, 300 μg subcutaneously given on days 8 through 15.	
Hydration (1,500-2,000 mL) of fluids IV given after ifosfamide.	
Frustaci S, Gherlinzoni F, De Paoli A, et al: J Clin Oncol 19:1238–1247, 2001.	
MAID	
Mesna	2.5 mg/m^2/d IV infused continuously over 24 hours on days 1-4
Adriamycin (doxorubicin)	20 mg/m^2/d IV infused continuously over 24 hours on days 1-3
Ifosfamide	2.5 g/m^2/d IV infused continuously over 24 hours on days 1-3
Dacarbazine	300 mg/m^2/d IV infused continuously over 24 hours on days 1-3
Repeat cycle every 21 days.	
Elias A, Ryan L, Sulkes A, et al: J Clin Oncol 7:1208–1216, 1989.	
Gemcitabine and docetaxel*	
Gemcitabine	900 mg/m^2 IV on days 1 and 8
Docetaxel	100 mg/m^2 on day 8
Repeat cycle every 21 days.	
NOTE: Granulocyte colony-stimulating factor is given subcutaneously on days 9 and 15. Patients who have undergone prior pelvic radiation therapy receive 25% dose reduction of both agents. Gemcitabine is delivered over 30 to 90 minutes in cycles 1 and 2 and by 90-minute infusion in all subsequent cycles. * This regimen is still under study.	
Hensley ML, Maki R, Venkatraman E, et al: J Clin Oncol 20:2824–2831, 2002.	

Table prepared by Ishmael Jaiyesimi, DO

alkylating agent, dacarbazine, or both agents. Overall, response rates are higher in these single-arm trials than when the same regimens are tested in larger, randomized studies.

AD and CyVADIC regimens The combination of Adriamycin (doxorubicin) plus dacarbazine (AD regimen) has been studied extensively (Table 2). Also, for over a decade, the CyVADIC regimen was widely accepted as the standard of care. In a prospective, randomized trial, however, CyVADIC did not prove to be superior to doxorubicin alone.

Doxorubicin (or epirubicin) plus ifosfamide Combinations of doxorubicin (or epirubicin) plus ifosfamide have consistently yielded responses in over 25% of patients in single-arm trials. In sequential trials conducted by the EORTC, doxorubicin at 75 mg/m^2 plus ifosfamide (5 g/m^2) was superior to doxorubicin at 50 mg/m^2 plus ifosfamide (5 g/m^2). A prospective randomized EORTC trial with 314 patients compared the two regimens. There was no difference in response rate or overall survival, but disease progression-free survival favored the more intensive regimen.

The strategy of intensifying the dosing of ifosfamide within the context of combination chemotherapy was explored in a randomized phase II trial. This study included both patients with localized disease treated with four cycles of preoperative chemotherapy as well as patients with metastatic disease. Overall, there was no survival benefit for patients treated with doxorubicin (60 mg/m^2) plus 12 g/m^2 of ifosfamide over those treated with doxorubicin (60 mg/m^2) plus 6 g/m^2 of ifosfamide. Also, there was no advantage to the patients with localized disease in terms of disease-free survival.

MAID regimen The MAID regimen (mesna, Adriamycin [doxorubicin; 60 mg/m^2], ifosfamide [7.5 g/m^2], and dacarbazine [900 mg/m^2], all given over 3 days; Table 2) yielded an overall response rate in 47% of patients in a large phase II trial. In a randomized comparison of AD vs MAID regimens, the response to MAID was 32%, vs 17% with the two-drug regimen ($P < .002$). However, the price paid for the higher response was toxicity; of 8 toxic deaths reported in this trial, 7 occurred among the 170 patients treated with MAID. All treatment-related deaths occurred in patients > 50 years old. During the study, the doses of MAID were reduced to lessen toxicity. Median survival did not differ significantly between the two regimens, although a trend favoring the AD regimen was noted.

Combination chemotherapy vs single-agent doxorubicin Combination chemotherapy has been compared with single-agent doxorubicin in eight randomized phase III trials. Two trials were limited to patients with uterine sarcoma. Some of these studies showed superior response rates with combination chemotherapy, but none of the trials found a significant survival advantage. Kaplan-Meier plots of survival are virtually superimposable within each trial and from trial to trial.

It should be emphasized that approximately 20%-25% of patients entered into such trials are alive 2 years after therapy was initiated. Complete responses are uncommon and do not appear to translate into prolonged survival.

Gemcitabine plus docetaxel In a phase II study of 34 patients with unresectable leiomyosarcoma, mostly uterine in origin, 53% responded to a combination of gemcitabine (given by 90-minute infusion) plus docetaxel (Taxotere), with filgrastim support. An additional 20% had stable disease. Almost half of the patients had disease progression after anthracycline-based therapy. The median time to disease progression was 5.6 months, and grade 3-4 toxicity was uncommon. A prospective, randomized trial comparing this regimen with gemcitabine alone in a spectrum of histologic types of sarcoma is ongoing.

Intensifying chemotherapy Hematopoietic growth factors have facilitated the evaluation of dose-intensive chemotherapy in patients with sarcoma. The nonhematologic toxicities (cardiac, neurologic, and renal) of the agents most active in soft-tissue sarcoma prevent dramatic dose escalation.

Phase I and II trials of dose-intense anthracycline/ifosfamide regimens with hematopoietic growth factor support have shown that doxorubicin (70-90 mg/m^2) can be used in combination with ifosfamide (10-12 g/m^2) in selected patients. Response rates as high as 69% have been reported. Although toxicity increases, often dramatically, with these relatively modest dose escalations, the clinical benefit in terms of survival or palliation in patients with metastatic disease remains uncertain.

No randomized trial has demonstrated a survival advantage for patients treated with these more aggressive regimens. In one randomized trial, however, the French Federation of Cancer Centers Sarcoma Group demonstrated that, in comparison with standard doses, a 25% escalation in doses of MAID with G-CSF support did not improve outcome.

High-dose therapy with autologous stem-cell transplantation. Most trials are small and presumably involve highly selected patients. In one recent trial involving 30 patients with metastatic or locally advanced sarcoma accrued over a period of 6 years, more than 20% were free of disease progression at 5 years after high-dose therapy with stem-cell rescue. Complete response to standard induction chemotherapy predicted superior 5-year survival. Based on these favorable results, the investigators suggested a prospective randomized trial examining this approach. Although some groups are still exploring this approach, the appropriateness of generalizing these results to most patients with soft-tissue sarcoma remains speculative.

Prognostic factors for response to therapy Over the past 20 years, the EORTC has collected data on more than 2,000 patients with metastatic disease who participated in first-line anthracycline-based chemotherapy trials. Multivariate analysis of these data indicated that the patients most likely to respond to chemotherapy are patients without liver metastases ($P < .0001$), younger patients, individuals with high histologic grade, and those with liposarcoma. In this Cox model, the factors associated with superior survival were good performance status, absence of liver metastases, low histologic grade, a long time to metastasis after treatment of the primary tumor, and young age.

More recently, these same investigators have reported that the observed response rate is superior in patients who have pulmonary metastases only, as compared with those who have metastases to the lungs and other sites or to other sites only. These findings highlight the danger of reaching broad conclusions based on extrapolations from small trials that include highly selected patients. The EORTC data are also consistent with the observation that patients with metastatic GI sarcoma rarely respond to standard chemotherapy regimens. This increasingly recognized observation has been used to explain the low response rates seen in some trials.

The French Sarcoma Group has initiated a phase III randomized trial looking at intermittent vs continuous imatinib therapy after completion of 1 year of continuous imatinib therapy. A total of 159 patients have enrolled in the trial. A partial or complete response was achieved in 52% of patients. Twenty-three patients were randomized to join the intermittent arm and 23, the continuous arm. After 3 months, 5 patients (21%) in the intermittent arm had evidence of disease progression, vs no patients in the continuous arm. Reintroduction of imatinib resulted in tumor control in all patients (*Blay JY, Berthaud D, Perol D, et al: J Clin Oncol [abstract] 22:14S, 2004*).

Targeted therapy for GISTs

Advances in our understanding of the biology of GIST, and the availability of an effective therapy for patients with advanced disease, have resulted in intense interest in this entity and rapid expansion of this disease. Because this entity had not been recognized, the incidence of GIST was underappreciated. GIST is the most common nonepithelial tumor of the gastrointestinal tract, with an estimated annual incidence of several thousand cases in the United States. Approximately 50%-60% of GISTS arise in the stomach and 25% in the small bowel. Other sites include the rest of the gastrointestinal tract, the omentum, mesentery, and retroperitoneum. These tumors may range in size from millimeters to huge masses.

Histologically, most are spindle cell lesions, but 20% may be predominantly epithelioid, and some have mixed features. Mitotic activity may range from very low to quite high. More than 95% stain positive for CD117, a marker of *KIT*, a transmembrane receptor with tyrosine kinase activity. In addition, 80% of GISTs are positive for BCL-2; 70%, for CD34; 50%, for muscle-specific actin; and 35%, for smooth muscle actin. Staining for desmin is uncommon (< 5%). It is thought that GISTs are related to the *KIT*-positive interstitial cells of Cajal, the pacemaker cells of the myenteric plexus. Prognosis for patients whose primary tumor is resected is related to size and mitotic activity.

The demonstration of the efficacy of imatinib (Gleevec) in GIST has been among the most dramatic and exciting observations in solid-tumor oncology. A randomized multicenter trial evaluated two doses of oral imatinib (400 vs 600 mg) in 147 patients with advanced GISTs. With median follow-up of 288 days, 54% had a partial response, and 28% had stable disease, but there were no complete responses. Response was sustained, with a median duration over 6 months. Most patients had mild grade 1 or 2 toxicity, but only 21% had severe grade 3 or 4 toxicity. GI or intra-abdominal hemorrhage occurred in 5% of patients. There was no difference in response or toxicity between the two doses.

These observations were expanded in two parallel, multi-institution trials in which patients with GISTs were randomized to receive imatinib (400 or 800 mg daily). The results were remarkably similar. In the American trial, among 746 registered patients, the overall response rate was 43% for patients treated with 400 mg and 41% for those treated with 800 mg. There were no differences in survival between the two arms. At 2 years, disease progression-free and overall survival rates in the 400-mg arm were 50% and 78%, respectively, In the 800-mg arm, the rate of disease progression-free survival at 2 years was 53% , and the rate of overall survival was 73%.

In a large European trial, 946 patients were randomized to receive imatinib (400 mg daily or bid). Among the 615 patients whose response could be evaluated, there was no difference in response frequency (43%) or survival between the two arms. Complete responses were seen in 3% and 2% of the lower-dose and higher-dose patients, respectively. Sixty-nine percent of patients progressing on 400 mg of imatinib were allowed to cross over to the higher dose (800 mg). Further therapeutic activity was seen, with 26% of these patients free of disease progression at 1 year.

In an analysis of prognostic factors for toxicity and response, the investigators found that the toxicity profile was related to initial levels of hemoglobin and albumin. Furthermore, toxicity was dose-dependent. Favorable disease progression-free survival was associated with good performance status, high hemoglobin level, gastric origin, and hepatic lesions.

Among a group of 127 patients with advanced GISTs, activating mutations of KIT or PDGFRA (platelet-derived growth factor receptor-alpha) were identified in 87.4% and 3.9% of patients, respectively. In patients harboring an exon 11 mutation of KIT, the partial remission rate was 83.5%, whereas in patients without a discernible mutation in KIT or PDGFRA, the partial remission rate was 9.1%. The presence of an exon 11 mutation in KIT correlated with clinical response, decreased risk of treatment failure, and improved overall survival.

The National Comprehensive Cancer Network (NCCN) recently established a GIST Task Force to develop guidelines for the evaluation and treatment of patients with GIST. This group recommended 400 mg daily as the initial starting dose of imatinib. Dose escalation should be considered in patients who do not respond initially or who demonstrate unequivocal disease progression. Surgery remains the primary modality for treatment of primary GIST, but adjuvant and neoadjuvant trials are ongoing. The efficacy, dose, and duration of imatinib therapy in these settings have not been established, so participation of patients in such trials should be encouraged.

Assessment of response and treatment after disease progression on imatinib The use of standard (RECIST) response criteria in patients with GIST may be misleading. On CT or MR imaging, large tumor masses may become completely necrotic without a reduction in size for months in spite of dramatic clinical improvement. Indeed, such masses may actually increase in size. ^{18}FDG (^{18}fluorodeoxyglucose) PET imaging may be extremely useful in selected patients, since response may be seen as early as 24 hours after a dose of imatinib. It should be noted that the survival of patients with stable disease parallels the survival of patients with major objective responses using RECIST criteria.

Surgery does not cure GIST that recurs after resection of primary disease and should be managed as metastatic disease. However, multimodality therapy should be considered in patients with limited sites of disease. It has also been recognized that patients with disease progression in limited sites of disease, occasionally with a growing nodule within a previously necrotic metastasis, may experience rapid disease progression of previously controlled areas. Thus, imatinib should be continued indefinitely in such patients, who should be referred for investigational therapy.

Studies of the genomic and biochemical profiles of GISTs suggest that essential downstream kinases may remain activated in patients with GISTs resistant to imatinib mesylate. Thus, it is notable that SU11248, a small molecule kinase inhibitor that targets multiple tyrosine kinases, has demonstrated promising clinical activity in patients with GISTs.

Recommendations for the treatment of metastatic sarcoma

- For patients with rapidly progressive disease or with symptoms, combination chemotherapy with an anthracycline/ifosfamide combination is indicated. For most patients, however, sequential single-agent therapy is less toxic and not inferior in terms of survival.
- The importance of histology relevant to selection of therapy is increasingly being appreciated. It is especially important to distinguish GISTs from GI leiomyosarcomas. Patients with suspected GIST should be referred to subspecialty centers experienced in the multimodality management of this disease.
- Periods of watchful waiting may be appropriate for many patients with metastatic sarcoma who have no or only minimal symptoms.

SUGGESTED READING

Alektiar KM, Leung D, Zelefsky MJ, et al: Adjuvant brachytherapy for primary high-grade soft-tissue sarcoma of the extremity. Ann Surg Oncol 9:48–56, 2002.

Burton GV, Rankin C, Flaherty LE, et al: Phase II trial of gemcitabine as first line chemotherapy in patients with metastatic or unresectable soft tissue sarcomas (STS) (abstract). Proc Am Soc Clin Oncol 22:820, 2003.

Coindre JM, Terrier P, Guillou L, et al: Predictive value of grade for metastasis development in the main histologic types of adult soft-tissue sarcomas: A study of 1,240 patients from the French Federation of Cancer Centers Sarcoma Group. Cancer 91:1914–1926, 2001.

Corless CL, Fletcher JA, Heinrich MC, et al: Biology of gastrointestinal stromal tumors. J Clin Oncol 22:3813–3825, 2004.

DeLaney TF, Spiro IJ, Suit HD, et al: Neoadjuvant chemotherapy and radiotherapy for large extremity soft-tissue sarcomas. Int J Radiat Oncol Biol Phys 56:1117–1127, 2003.

Eilber FC, Rosen G, Nelson SD, et al: High-grade extremity soft-tissue sarcomas: Factors predictive of local recurrence and its effect on morbidity and mortality. Ann Surg 237:218–226, 2003.

Fletcher JA, Corless CL, Dimitrijevic S, et al: Mechanisms of resistance to imatinib mesylate (IM) in advanced gastrointestinal stromal tumor (GIST) (abstract). Proc Am Soc Clin Oncol 22:815, 2003.

Fletcher CD, Gustafson P, Rydholm A, et al: Clinicopathologic re-evaluation of 100 malignant fibrous histiocytomas: Prognostic relevance of subclassification. J Clin Oncol 19:3045–3050, 2001.

Frustaci S, Gherlinzoni F, De Paoli A, et al: Adjuvant chemotherapy for adult soft-tissue sarcomas of the extremities and girdles: Results of the Italian randomized cooperative trial. J Clin Oncol 19:1238–1247, 2001.

Gieschen HL, Spiro IJ, Suit HD, et al: Long-term results of intraoperative electron-beam radiotherapy for primary and recurrent retroperitoneal soft-tissue sarcoma. Int J Radiat Oncol Biol Phys 50:127–131, 2001.

Hensley ML, Maki R, Venkatraman E, et al: Gemcitabine and docetaxel in patients with unresectable leiomyosarcoma: Results of a phase II trial. J Clin Oncol 20:2824–2831, 2002.

Kasper B, Meissner J, Harter C, et al: High-dose chemotherapy (HDCT) with autologous peripheral blood stem cell transplantation (PBSCT) for bone and soft tissue sarcomas (abstract). Proc Am Soc Clin Oncol 22:817, 2003.

Kattan MW, Leung DH, Brennan MF: Postoperative nomogram for 12-year sarcoma-specific death. J Clin Oncol 20:791–796, 2002.

Kraybill WG, Spiro I, Harris J, et al: Radiation Therapy Oncology Group (RTOG) 95-14: A phase II study of neoadjuvant chemotherapy (CT) and radiation therapy (RT) in high-risk (HR), high grade, soft-tissue sarcomas (STS) of the extremities and body wall: A preliminary report (abstract). Proc Am Soc Clin Oncol 20:348, 2001.

Le Cesne A, Blay J, Judson I, et al: ET-743 is an active drug in adult soft-tissue sarcoma (STS): A STBSG-EORTC phase II trial (abstract). Proc Am Soc Clin Oncol 20:353, 2001.

Le Cesne A, Judson I, Crowther D, et al: Randomized phase III study comparing conventional-dose doxorubicin plus ifosfamide vs high-dose doxorubicin plus ifosfamide plus recombinant human granulocyte-macrophage colony-stimulating factor in advanced soft-tissue sarcomas: A trial of the European Organization for Research on the Treatment of Cancer/Soft-Tissue and Bone Sarcoma Group. J Clin Oncol 18:2676–2684, 2000.

Noorda EM, Vrouenraets BC, Nieweg OE, et al: Isolated limb perfusion with tumor necrosis factor-alpha and melphalan for patients with unresectable soft tissue sarcoma of the extremities. Cancer 98:1483–1490, 2003.

O'Sullivan B, Bell RS, Bramwell VHC: Sarcomas of the soft tissues, in Souhami RL, Tannock I, Hohenberger P, et al (eds): Oxford Textbook of Oncology, 2nd ed, pp 2495–2523. Oxford, Oxford University Press, 2002.

O'Sullivan B, Davis A, Turcotte R, et al: Five-year results of a randomized phase III trial of preoperative vs post-operative radiotherapy in extremity soft tissue sarcoma (abstract). Proc Am Soc Clin Oncol 22:14S, 2004.

O'Sullivan B, Davis AM, Turcotte R, et al: Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: A randomized trial. Lancet 359:2235–2241, 2002.

Pisters PW, Patel SR, Prieto VG, et al: Phase I trial of preoperative doxorubicin-based concurrent chemoradiation and surgical resection for localized extremity and body wall soft tissue sarcomas. J Clin Oncol 22:3375–3380, 2004.

Riad S, Griffin AM, Liberman B, et al: Lymph node metastasis in soft tissue sarcoma in an extremity. Clin Orthop Sep:129–134, 2004.

Rubin BP, Singer S, Tsao C, et al: KIT activation is a ubiquitous feature of gastrointestinal stromal tumors. Cancer Res 61:8118–8121, 2001.

Trovik CS, Bauer HC, Alvegard TA, et al: Surgical margins, local recurrence, and metastasis in soft-tissue sarcomas: Five hundred fifty-nine surgically treated patients from the Scandinavian Sarcoma Group Register. Eur J Cancer 36:710–716, 2000.

Van den Abbeele AD, Badawi RD Cliche J-P, et al: ^{18}F-FDG-PET predicts response to imatinib mesylate (Gleevec) in patients with advanced gastrointestinal stromal tumors (GIST) (abstract). Proc Am Soc Clin Oncol 21:403, 2002.

Van Glabbeke MM, Verweij J, Casali PG, et al: Prognostic factors of toxicity and efficacy in patients with gastro-intestinal stromal tumors (GIST) treated with imatinib: A study of the EORTC-STBSG, ISG, and AGITG (abstract). Proc Am Soc Clin Oncol 22:818, 2003.

Wendtner C-M, Abdel-Rahman S, Krych M, et al: Response to neoadjuvant chemotherapy combined with regional hyperthermia predicts long-term survival for adult patients with retroperitoneal and visceral high-risk soft-tissue sarcomas. J Clin Oncol 20:3156–3164, 2002.

Worden FP, Taylor JMG, Bierman JS, et al: A randomized phase II evaluation of standard dose ifosfamide (IFOS) plus doxorubicin (DOX) versus high dose ifosfamide plus DOX in patients with high-grade soft tissue sarcomas (abstract). Proc Am Soc Clin Oncol 22:817, 2003.

Zalcberg JR, Verweij J, Casali PG, et al: Outcome of patients with advanced gastrointestinal stromal tumors (GIST) crossing over to a daily imatinib dose of 800 mg (HD) after progression on 400 mg (LD)–An international, intergroup study of the EORTC, ISG, and AGITG (abstract). Proc Am Soc Clin Oncol 22:819, 2004.